

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 93616-2	<div style="display: flex; justify-content: space-between;"> FOR FURTHER ACTION See Form PCT/IPEA/416 </div>	
International application No. PCT/CA2004/001431	International filing date (<i>day/month/year</i>) 30 July 2004 (30-07-2004)	Priority date (<i>day/month/year</i>) 30 July 2003 (30-07-2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07C 255/38, C07D 213/71, C07C 255/32, A61K 31/277, A61K 31/4402, A61P 35/00		
Applicant THE HOSPITAL FOR SICK CHILDREN ET AL		
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>2</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. <input type="checkbox"/> (<i>sent to the applicant and to the International Bureau</i>) a total of _____ sheets, as follows: <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. 1 and the Supplemental Box. b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).		
4. This report contains indications relating to the following items: <div style="margin-left: 20px;"> <input checked="" type="checkbox"/> Box No. I Basis of the report <input checked="" type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input checked="" type="checkbox"/> Box No. VII Certain defects in the international application <input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application </div>		
Date of submission of the demand 11 May 2005 (11-05-2005)	Date of completion of this report 25 October 2005 (25-10-2005)	
Name and mailing address of the IPEA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer <div style="text-align: right;">Okemona Oke (819) 956-4108</div>	

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/001431

Box No. I Basis of the report

1. With regard to the language, this report is based on:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
 - ☐ international search (Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (Rule 12.4(a))
 - ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))
2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
 - ☒ the international application as originally filed/furnished
 - ☐ the description:
 - ☐ pages _____ as originally filed/furnished
 - ☐ pages* _____ received by this Authority on _____
 - ☐ pages* _____ received by this Authority on _____
 - ☐ the claims:
 - ☐ pages _____ as originally filed/furnished
 - ☐ pages* _____ as amended (together with any statement) under Article 19
 - ☐ pages* _____ received by this Authority on _____
 - ☐ pages* _____ received by this Authority on _____
 - ☐ the drawings:
 - ☐ pages _____ as originally filed/furnished
 - ☐ pages* _____ received by this Authority on _____
 - ☐ pages* _____ received by this Authority on _____
 - ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages _____
 - ☐ the claims, Nos. _____
 - ☐ the drawings, sheets/figs _____
 - ☐ the sequence listing *(specify)*: _____
 - ☐ any table(s) related to sequence listing *(specify)*: _____
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages _____
 - ☐ the claims, Nos. _____
 - ☐ the drawings, sheets/figs _____
 - ☐ the sequence listing *(specify)*: _____
 - ☐ any table(s) related to sequence listing *(specify)*: _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The validity of the priority claim has been established because the International Searching Authority has in its possession a copy of the earlier application on which priority has been claimed.

**INTERNATIONAL PRELIMINARY REPORT ON
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non

☐ the entire international application

☒ claims Nos. 17-19, 35-37

because:

☒ the said international application, or the said 17-19, 35-37

relate to the following subject matter which does not require an international preliminary examination

Although claims 17-19 and 35-37 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.

☐ the description, claims or drawings (*indicate particular elements below*) or said are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims are so inadequately by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Instructions, and such listing was not available to the International Preliminary Examining

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C Administrative Instructions, and such listing was not available to the International Preliminary

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an Rules 13^{ter}.1(a) or (b) and 13^{ter}.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

**INTERNATIONAL PRELIMINARY REPORT ON
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International application No.
PCT/CA2004/001431

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial

1. Statement

Novelty (N)	Claims	2, 6-19, 29	YES
	Claims	1, 3-5, 20-28, 30-37	NO
Inventive step (IS)	Claims		YES
	Claims	1-37	NO
Industrial applicability	Claims	1-16, 20-24	YES
	Claims	17-19, 35-37	NO

2. Citations and explanations (Rule 70.7)

The following references are considered relevant:

D1: WO-A- 0179158 (ROIFMAN, C, ET AL)

D2: WO-A-9524190 (CHEN, H, ET AL)

D3: US-5,789,427 (CHEN, H, ET AL)

D4: WO-A-9640629 (TANG, P, ET AL)

D5: US-3,718,472 (OLIVER, G.L. ET AL)

D6: JP-2001066605 (SAKAI, ET AL)

D7: CA-1,264,594 (PATEL, ET AL)

D8: CHINESE CHEMICAL LETTERS. (ZHONG, ET AL)

NOVELTY

The application relates to a class of compounds, represented by Formulas I and III, which are useful for treating cell proliferative disorders. The compounds generally comprise, in Formula I, aralkyl or aryloxyalkyl derivatives of acid esters bearing the terminal group -X-R⁴ and in Formula III, alkyl-, phenyl- or pyridinosulphonyl derivatives bearing the terminal group R⁴. In the closest art, document D1, compounds analogous to Formula I of the instant invention are disclosed, except that -X-R⁴ is C₁-C₅ alkyl or H (see especially compounds CR14 and CR15, claims 21 and 22). Also, are disclosed, a class of compounds defined by a general formula of the same scope as Formula III of the instant invention wherein R⁴ is phenyl optionally substituted with substituents selected from, *inter alia*, alkyl, alkoxy and halo (see claims 1-8, 16-20 and 27-43). Accordingly, at the very least, the document D1 is novelty destroying with respect to present claims 20-28 and 30-37. (see supplemental sheet)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

*International application No.
PCT/CA2004/001431*

Box No. VII *Certain defects in the international application*

The following defects in the form or contents of the international application have been noted:

Article 5 PCT Objections

If the terms “Kieselgel” and “Zorbax” in page 23 are trademarks, they should be so indicated.

Claims 32-34 should be renumbered such that they are grouped with claims 1-19 as the present format unnecessarily obscures the definition of subject matter for which protection is sought (Rule 6.4(c)).

Box No. VIII ***Certain observations on the international application***

The following observations on the clarity of the claims, description, and drawings or on the question whether

Article 6 PCT Objections

In claims 2, 8 and 9, the definition of R⁴ as C₁₋₆ alkyl is not within the scope of claim 1 where R⁴ is limited to Ar or substituted Ar (see page 2 line 6-15, page 10 line 10, Formula (II)).

In claims 1 and 6, the character "Ar" is not defined.

In claims 14, 17, 32 and 35, the term "and/or" is ambiguous and avoidably obscures the inventive scope.

Claims 14, 17, 32 and 35 do not comply with Article 6 PCT because the description fails to provide a sound line of reasoning for the utility of the defined compounds for modulating cell proliferation. As described in the current description, the verb "modulate" includes the inhibition or suppression of a function or activity as well as the enhancement of a function or activity. While the description provides a factual basis on which to support the utility of the defined compounds in inhibiting or suppressing cell proliferation, there is no such factual support for the utility of the defined compounds for enhancing cell proliferation.

To enhance clarity, in claim 22, insert "wherein" between "21" and "and R¹".

In claim 32, no process step is specified. As worded, claim 32 attempts to define the invention by a result to be achieved rather than by the specific process steps taken to achieve the desired result. Also, the subject matter claim 32, insofar as specific process steps are not indicated, is broader than the invention as described.

The statement in page 27 line 11-13 which refers to certain unspecified embodiments of the invention as within the spirit of the invention attempts to unfairly and vaguely expand the inventive scope beyond the explicit teachings as set forth in the specification (Article 6 PCT). This statement is clearly irrelevant and unnecessary under the circumstances and should be removed (Rule 9.1 (iv) PCT).

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation **Box No. V**

Document D5 discloses a class of compounds and composites thereof which fall within the scope of Formula III wherein R^4 is alkyl or phenyl and R^2 is substituted amino (see col 1 line 35 to col 2 line 12, col 6 line 1-10, claims 1 and 8, Example 5), thus D5 is novelty destroying with respect to present claims 20-21 and 23-27. Document D6 discloses 2,4-pentanedienoic acid, 2-cyano-5-phenyl-2-[4'-[6-(2-methyl-1-oxo-2-propenyl)-oxy]hexyl]1,1'-biphenyl]-4-yl] oxy] ethyl ester which fall within the scope of instant claims (present formula I wherein R^1 , R^2 and R^3 are H, X is CH_2CH_2O- , R^4 is aryl substituted with alkoxy). Document D6 is novelty destroying in respect of claims 1, 3, 4 and 5.

INVENTIVE STEP

The problem posed by the present invention resides in the provision of compounds that can inhibit or modulate cell proliferation which have practical applications in cancer treatment. This is solved by the present acid ester and sulphonyl derivatives as broadly defined by Formulas I and III. As noted earlier, compounds that fall within the scope of present Formula I have been disclosed by D1. Documents D2, D3 (see especially Figures 1A, 2B, 2D, 3A, 3C, 3E to 3L; col 5 line 4-24, col 43 line 18-30, col 43 line 55 to col 44 line 13, M26, M30, M31, M32-M34, Table 1 and Table 4) and D4 (see especially, pages 4-6, compounds 731, 740, 741, 744, 748, Examples 4, 5, 7, 18, 20, 27, 34, 42-47 and 60-82, 84, 86-88 and 90-93, Table 1 & 2, claims 1, 5, 7, 11 and 14-17), disclose various structurally close or substitutional alternatives to the present compounds for use in treating cell proliferative disorders. The use, in the present invention, of the substitutional alternative and functional bioequivalent aryl or aryloxy groups, more specifically, the apparent elaboration of the H or alkyl group in the acid esters of D1, as in present claims 1-19 is within the consideration and purview of the skilled person during the normal course of experimentation. Accordingly, claims 1-19 are obvious having regard to D1 in view of D2-D4 under Article 33.2 PCT.

Documents D2-D4 also disclose sulphonyl derivatives or analogous of present Formula III with the exception of the presence of an alternative linker $-CH=CH-CH=CH-$. However, compounds bearing said linker are disclosed in D1. A person skilled in the art desiring to make alternatives of the sulphonyl derivatives of D2-D4 would, with expectation of success, have considered embodiments containing the alternative linker $-CH=CH-CH=CH-$ such as disclosed in D1. Thus, the subject matter of claims 20-37 would have been obvious having regard to teachings of D2, D3 or D4 in combination with D1. In any case, it is not shown, in the present description, any comparative data which points to an unexpected technical advantage of the present compounds over those disclosed in the art. Accordingly, an inventive step cannot be acknowledged for present claims 1-37 under Article 33.3 PCT. Document D7 discloses 4-dimethylaminophenyl methanesulfonyl derivatives of present Formula III. Document D8 discloses 3-nitrophenyl-, 4-chlorophenyl-, phenyl and 4-methoxyphenyl derivatives sulfonyl derivatives of present Formula III. The formulation of these compounds into compositions in the presence of conventional adjuvants would be obvious to a person skilled in the art and does not require an exercise of inventive ingenuity. Thus, claims 30-31 are not inventive over documents D7 and D8.

(see supplemental Box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation Box No. V

INDUSTRIAL APPLICABILITY

Claims 1-16 and 20-34 are directed to subject matter considered as fulfilling the requirements set forth under Article 33(4) PCT. For the assessment of present claims 17-19 and 35-37 under Article 33(4) PCT, on whether it is industrially applicable, no unified criteria exists in the PCT. The patentability can also be dependent upon the formulation of claims.

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